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## Temporal reproduction and its neuroanatomical correlates in adults with Attention Deficit Hyperactivity disorder and their unaffected first degree relatives

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Abstract</b></p> <p><b>Background</b></p> <p>Little is known about time perception, its putative role as cognitive endophenotype, and its neuroanatomical underpinnings in adults with Attention Deficit Hyperactivity Disorder (ADHD).</p> <p><b>Methods</b></p> <p>20 adults with ADHD, 20 unaffected first degree relatives and 20 typically developing controls matched for age and gender undertook structural magnetic resonance imaging (MRI) scans. Voxel-based morphometry (VBM) with DARTEL was performed to obtain regional grey matter volumes. Temporal processing was investigated as a putative cognitive endophenotype using a temporal reproduction paradigm. General linear model was employed to examine the relationship between temporal reproduction performances and grey matter volumes.</p> <p><b>Results</b></p> <p>ADHD participants were impaired in temporal reproduction and unaffected first degree relatives performed in between their ADHD probands and typically developing controls. Increased grey matter volume in the cerebellum was associated with poorer temporal reproduction performance.</p> <p><b>Conclusions</b></p> <p>Adults with ADHD are impaired in time reproduction. Performances of the unaffected first degree relatives are in between ADHD relatives and controls, suggesting that time reproduction might be a cognitive endophenotype for adult ADHD. The cerebellum is involved in time reproduction and might play a role in driving time performances.</p>

# **Temporal reproduction and its neuroanatomical correlates in adults with Attention Deficit Hyperactivity disorder and their unaffected first degree relatives**

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## **Abstract**

### Background

Little is known about time perception, its putative role as cognitive endophenotype, and its neuroanatomical underpinnings in adults with Attention Deficit Hyperactivity Disorder (ADHD).

### Methods

20 adults with ADHD, 20 unaffected first degree relatives and 20 typically developing controls matched for age and gender undertook structural magnetic resonance imaging (MRI) scans. Voxel-based morphometry (VBM) with DARTEL was performed to obtain regional grey matter volumes. Temporal processing was investigated as a putative cognitive endophenotype using a temporal reproduction paradigm. General linear model was employed to examine the relationship between temporal reproduction performances and grey matter volumes.

### Results

ADHD participants were impaired in temporal reproduction and unaffected first degree relatives performed in between their ADHD probands and typically developing controls. Increased grey matter volume in the cerebellum was associated with poorer temporal reproduction performance.

### Conclusions

Adults with ADHD are impaired in time reproduction. Performances of the unaffected first degree relatives are in between ADHD relatives and controls, suggesting that time reproduction might be a cognitive endophenotype for adult ADHD. The cerebellum is involved in time reproduction and might play a role in driving time performances.

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders in childhood and adolescence (Kieling *et al.*, 2010) and is one of the most underdiagnosed psychiatric disorders in adults (Faraone, 2007). It is defined with age inappropriate symptoms of hyperactivity/impulsivity and inattention, and with functional impairments in social, family and school/work settings.

Evidence shows that adults with ADHD commonly present with neurocognitive impairments in several domains, including response inhibition, delay aversion, working memory, sustained attention, time processing, and motivational processes (Seidman *et al.*, 2004).

One area of neuropsychological performance not well studied in adults with ADHD is time perception. Sense of time is a multidimensional construct encompassing perceiving the passing of moments from one to another, organizing a sequence of actions, and predicting when future events will occur (Toplak *et al.*, 2006). Thus far, the majority of the research exploring time processing impairments in ADHD has been conducted in children showing impairments in temporal processing domains including time production (Van Meel *et al.*, 2005), motor timing (Rubia *et al.*, 2003, 1999), time perception (Smith *et al.*, 2002, Yang *et al.*, 2007) and time reproduction (Barkley *et al.*, 1997, Bauermeister *et al.*, 2005, Rommelse *et al.*, 2007). However, research has shown that time reproduction deficits are the most consistent timing problems found in children and adolescents with ADHD (Barkley, 2006, Barkley *et al.*, 2001a, Bauermeister *et al.*, 2005, Toplak *et al.*, 2006). In a typical reproduction task a light bulb presented on a computer screen is switched on for different time durations, and then the participant must reproduce the sample duration using the same means (e.g. by switching on the light bulb and turning it off when they think the time duration has elapsed). In such paradigm children with ADHD show an increase in errors magnitude with the length of the time intervals to be reproduced (Bauermeister *et al.*, 2005,

Block *et al.*, 2010, West *et al.*, 2000). Seminal work by Barkley and colleagues (Barkley *et al.*, 1997) examined time reproduction performance taking into account also the effects of attentional demands and use of methylphenidate (MPH). While all children (both ADHD and controls) performed similarly at short durations, children with ADHD made significantly larger errors of reproduction than controls on intervals of 6, 10, and 16 seconds. In studies using supra-seconds intervals, children with ADHD showed a trend toward progressively greater time underestimation as the target time interval to be reproduced increased (Kerns *et al.*, 2001). Poor temporal reproduction performances seem to persist over time, as adolescents with ADHD are also impaired in time reproduction task compared to age matched controls (Barkley *et al.*, 2001a). As seen, abnormalities in reproducing temporal durations have been consistently documented in children with ADHD. However, there is still paucity of research in adults. One study showed that adults with ADHD also have poorer time reproduction abilities compared to typically developing controls (Barkley *et al.*, 2001b). Marx and colleagues showed that increasing age ameliorated time reproduction deficits in ADHD; however abnormalities persisted into adulthood in individuals with ADHD compared to controls (Marx *et al.*, 2010).

We know little about the neuroanatomical and neurophysiological correlates of time processing impairments in adult ADHD. In the only neuroimaging study examining time processing in adults with ADHD, using a finger tapping paradigm in age and IQ matched adults, Valera and colleagues found an atypical pattern of neural activity in the cerebellum and basal ganglia (Valera *et al.*, 2010).

In healthy individuals temporal information processing seems to engage multiple brain areas including the cerebellum, basal ganglia and prefrontal cortex (e.g. Ivry, 1996, Ivry *et al.*, 2002, Meck *et al.*, 2008). To our knowledge, there are no studies to date examining the association between neuroanatomical characteristics and time reproduction in adult ADHD. In this study we assessed the brain volumetric correlates of temporal reproduction performances in adults with ADHD, using voxel-based morphometry (VBM), focusing on one region of interest (ROI) including areas previously described having a role in timing, namely cerebellum, prefrontal cortex, and basal ganglia.

Investigating time reproduction abilities in adult ADHD might also contribute to the search of cognitive endophenotypes in adult ADHD, which in turn should progress the search for susceptibility genes for the disorder (Gottesman and Gould, 2003) and inform novel pharmacological and neurocognitive treatment discoveries based on a biomarker approach. Endophenotypes are defined as internal, quantitative traits closer to the expression of the genes than the clinical picture *per se*. If the clinical phenotype is reduced to its basic neurocognitive components, the number of genes associated with variation in endophenotype might be fewer compared with the number of genes linked to the overt clinical phenotype. Reducing the number of genes to test for should enhance the statistical power in molecular genetic studies aimed at discovering susceptibility genes for the disorder (Almasy and Blangero, 2001, Aron and Poldrack, 2005, Doyle *et al.*, 2005, Gottesman and Gould, 2003, Leboyer *et al.*, 1998). Time reproduction might meet several of the criteria for an endophenotype: heritable, associated with the disorder, and expressed at higher rates in unaffected relative of probands with ADHD than individuals drawn from the general population (Almasy and Blangero, 2001, Gottesman and Gould, 2003). It has been shown that children with ADHD and their unaffected siblings were both impaired in time

reproduction compared to controls (Rommelse *et al.*, 2007). Therefore, we further assessed whether time reproduction is a potential endophenotype in adult ADHD testing the hypothesis that first degree relatives of ADHD patients would share abnormalities in a temporal reproduction paradigm compared to unrelated controls. To our knowledge, this is the only study examining time reproduction deficits as a cognitive endophenotype in adult ADHD.

## **Methods**

### ***Participants***

We tested 20 adults with ADHD, 20 unaffected first degree relatives of adults with ADHD, and 20 typically developing control participants. Written consent was obtained from each participant. The study was approved by the Cambridgeshire 3 Research Ethics Committee (REC: 09/H0306/38). ADHD proband-relative pairs were recruited from the Adult ADHD Research Clinic, Addenbrooke's hospital, Department of Psychiatry, University of Cambridge. Patients received a diagnosis of ADHD according to DSM-IV-TR (APA, 2000), based on a full clinical interview with the patient and an informant who had known the patient since childhood. The clinical assessment also included rating scales: Barkley adult ADHD rating scale, self-report and informant report, childhood and adulthood symptoms (BAARS; Barkley, 2011), assessing childhood and adulthood symptoms from the perspective of the patient and the informant. Eligible patients were asked to contact a first degree relative who undertook the same clinical protocol to screen for undiagnosed ADHD in adulthood. Control participants were recruited via posters in the local community and underwent the same procedure.

On the testing day, all participants were interviewed using the Mini International Neuropsychiatric Inventory (Sheehan *et al.*, 1998) to screen for DSM-IV Axis I disorders,

and completed the Barkley adult ADHD rating scale, self-report, (BAARS; Barkley, 2011). Estimate of full IQ was obtained using the National Adult Reading Test (NART; Nelson and O'Connell, 1978). Neither controls nor first degree relatives of ADHD probands showed ADHD symptoms meeting the DSM-IV-TR diagnostic threshold for ADHD. Moreover, they did not show clinically significant symptoms of another DSM-IV-TR disorder. Finally, ADHD participants did not show relevant symptoms of a comorbid disorder reaching clinical significance for a formal DSM-IV-TR diagnosis. To reduce confounds resulting from other major psychiatric and neurological conditions, exclusion criteria were: i) full IQ  $\leq 90$ , ii) current or past history of pervasive developmental disorder, any neurological disorder (including tic disorders), bipolar disorder, substance-use disorders, schizophrenia or other psychotic disorders, iii) current major depressive disorder, and iv) contraindications to MRI scan. To minimize the impact of psychotropic medications on cognitive performance, participants were asked to omit taking those 24 hours before testing (Gualtieri *et al.*, 1982, Turner *et al.*, 2005) and were asked to refrain from consuming alcohol or caffeine-containing drinks on the day of testing. The ADHD group comprised 16 patients with combined type and 4 with inattentive type; 16 of them were ordinarily medicated with methylphenidate, and 4 did not receive medication for ADHD. None of the participants were excluded due to a NART full IQ below 90.

## **Cognitive task**

### ***Time reproduction task***

Participants were asked to reproduce sub-seconds and supra-seconds stimulus durations watching a computer screen where two lights bulbs appeared. After the top light bulb was switched on for a specific interval length, the bottom light bulb had to be kept lit for the same interval length by pressing the space bar continuously (this response is defined as response length). Following 4 practice trials, the task comprised 42 trials (6 per stimulus length) that



were randomly distributed. Stimulus durations were 500ms, 1000ms, 3000ms, 6000ms, 12000ms, 18000ms, and 24000ms.

The dependent variable was the absolute discrepancy score measured as the absolute discrepancy between the target duration and the reproduction provided by the subject (response length). We also calculated the omnibus absolute discrepancy score (i.e., the sum of the seven different absolute discrepancy score for each duration); the higher the score, the more impaired performance.

A repeated measure analysis of covariance (ANCOVA) was used with group as the fixed factor with three levels (ADHD, Relatives, Controls) and target duration as repeated measure (seven levels of durations in milliseconds: 500, 1000, 3000, 6000, 12000, 18000, 24000). Age and full IQ were included as covariates. Finally, since Mauchly's test of sphericity was always significant for target duration factor of the design, the Huynh-Feldt (HF) values for the F tests involving the duration factor was used. Given the number of comparisons a Bonferroni correction was applied; however, when Levene's test for equality of variance was significant, Tamhane correction was used.

### ***MRI acquisition***

Images were acquired at the Wolfson Brain Imaging Centre, University of Cambridge, UK, using a Siemens TIM Trio 3T system. T1-weighted MR scans were acquired using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (176 slices, 1mm thickness, TR = 2300ms, TE = 2.98ms, TI = 900ms, flip angle = 9°, FOV= 240 x 256) and manually aligned to the anterior commissure (AC) – posterior commissure (PC) line. Voxel-based morphometry (VBM) analysis was performed using SPM8 (Wellcome Department of Imaging Neuroscience, London). To improve the registration of the MRI images, we used the diffeomorphic anatomic registration through an exponentiated lie algebra algorithm (DARTEL) (Ashburner, 2007). DARTEL provides improved registration accuracy

compared with conventional VBM, and VBM with DARTEL is more sensitive than conventional VBM methods (Klein *et al.*, 2009). The following processing steps were implemented: 1) structural images of all 60 participants were included for creating a study-specific template; 2) structural images of each participant were segmented (using unified segmentation) and imported into DARTEL to create the study-specific template, while all images were warped to the study-specific template then into the standard MNI space; 3) Jacobian modulation was applied to preserve information about local volumes; and 4) images were smoothed with an 8 mm full-width at half maximum kernel. A correlation analysis between grey matter volume and the omnibus absolute discrepancy score across groups was performed in SPM8 (using GLM) with age and IQ included as covariates. We were interested in cortical areas previously found to be associated with time processing, for this reason one region of interest (ROI) was employed using WFU Pick-Atlas (Maldjian *et al.*, 2003), comprising prefrontal cortex, basal ganglia, and cerebellum. Only clusters surviving at FWE  $p < 0.05$  corrected at the cluster level, with a conservative voxel-level cluster-forming threshold,  $ac$  of 0.001 are reported.

To characterize differences between the 3 groups, cluster regional volume estimates surviving the correlation analyses were extracted using Marsbar (<http://marsbar.sourceforge.net/>; Brett *et al.*) and imported into SPSS (version 21; <http://www.spss.com/>) to perform ANOVA analyses, with group (ADHD, Relatives, Controls) as a fixed factor and cluster regional volume estimates as dependent variables. This ROI analysis methodology has been widely implemented in other studies (Carmona *et al.*, 2011, Egner and Hirsch, 2005). All brain coordinates are given in Montreal Neurological Institute convention (MNI). A Probabilistic MRI Atlas of the Human Cerebellum (Diedrichsen *et al.*, 2009) was used to assign anatomical labels to cerebellar structures.

## Results

### *Participant characteristics*

The 3 groups did not differ significantly in age and gender. ADHD group scored 4 points lower than typically developing controls on NART full IQ. ADHD group differed from relatives and controls in self-reported current and childhood ADHD symptoms. Unaffected first degree relatives were significantly different from ADHD and control groups on self-reported current hyperactive/impulsive symptoms, childhood total symptoms, childhood hyperactive/impulsive and inattentive symptoms (Table 1).

---Insert Table 1 about here---

### *Behavioural analysis*

Table 2 shows the mean and standard deviation of the time reproduction task performance (absolute discrepancy score).

---Insert Table 2 about here---

A main effect of group was found [ $F(2, 56) = 4.070, p = 0.009$ ] consistent with the hypothesis of ADHD performing significantly worse than the other groups. A main effect of duration [ $F(1.796, 100.566) = 10.057, p < 0.001$ ] was also found, indicating that performance deteriorated as interval length increased, reflecting effects of task difficulty. Moreover, a significant interaction between duration and group was also present [ $F(3.592, 100.566) = 4.627, p = 0.003$ ], suggesting that increasing interval length had differential effects for the three groups (Figure 1). Pairwise comparisons decomposing the main effect of group showed that the ADHD group was significantly worse in time reproduction than the control group ( $p = 0.010$ ), but first degree relatives were not significantly different from the ADHD group ( $p$

= 1.00). There was a trend difference in performance between first degree relatives and controls ( $p = 0.082$ ).

---Insert Figure 1 about here---

### ***Neuroimaging analysis***

MANCOVA analysis assessing for Total Intracranial Volume (TIV) and Total Brain Volume (TBV) with group as the fixed factor and age as a covariate showed no differences between the three groups for both variables TIV:  $F(2, 56) = 1.536$ ,  $p = 0.224$ ; TBV:  $F(2, 56) = 1.827$ ,  $p = 0.170$ .

Voxel-level GLM analysis within our ROI, covaried for age and full IQ, showed one significant cluster of 797 voxels surviving FWE cluster level correction at  $q < 0.05$  (Figure 2), where increased volume was correlated with increased absolute discrepancy score across groups (implying poorer time reproduction;  $r = 0.297$ ,  $p = 0.021$ ). This cluster was located in the cerebellum, at peak voxel centred on MNI coordinates  $x = 9$ ;  $y = -57$ ;  $z = -15$  (Right cerebellar lobule V). There were no significant results showing a negative correlation. Between group analysis showed no significant differences [ $F(2, 55) = 2.151$ ,  $p = 0.126$ ]. Decomposing the correlation using a bivariate analysis between grey matter volume estimates within this cluster and the absolute discrepancy score according to group showed that only the correlation within the ADHD group remained significant at  $p = 0.05$  (ADHD:  $r = 0.505$ ,  $p = 0.023$ ; Relatives:  $r = 0.121$ ,  $p = 0.613$ ; Controls:  $r = 0.079$ ,  $p = 0.740$ ), suggesting a role of grey matter variability in driving performance within the ADHD group.

---Insert Figure 2 about here---

### **Discussion**

One of the aims of this study was to test whether adults with ADHD were impaired in temporal information processing, specifically in a time reproduction paradigm. The results show that not only children with ADHD (Barkley *et al.*, 1997, Block *et al.*, 2010) but also

adults with ADHD suffer from time processing deficits. In addition, we also found that impairments in time reproduction were not mainly due to differences between ADHD and control samples in intellectual ability as the findings remained unchanged when the effect of IQ was held constant in the analysis. Overall, time reproduction is abnormal in adults with ADHD. Trend gender distribution differences between groups within our sample are unlikely to be the main driver for such significant differences in performances, as previously it was shown that in a large sample of individuals with ADHD followed for 7 years there was no evidence that gender moderated the association between ADHD and the phenotypic expression of the disorder, the prevalence of lifetime or current comorbid psychiatric disorders, or patterns of cognitive and psychosocial functioning (Biederman *et al.*, 2004).

At the neuroanatomical level, we found that across the whole sample, the main structure associated with temporal reproduction processing was at the cerebellum, rather than at the basal ganglia or prefrontal cortex. This suggests a substantial role of cerebellum in time reproduction abilities. More specifically, we found that an increase in grey matter volume in the right cerebellar lobule V was associated with worse performance in reproducing time durations. The present positive correlation in the ADHD group between grey matter volume in the cerebellum and time reproduction score is consistent with the hypothesis that an abnormal increase in grey matter volume in the lobule V of the cerebellum has a role in time reproduction deficits; however, this correlation becomes a trend without all data points included, and therefore this finding requires further replication. Nonetheless, this result is consistent with recent research highlighting a role of the cerebellum in temporal processing in the general population (Stoodley, 2012).

Despite that cerebellar neuroanatomical abnormalities in ADHD have been shown by previous studies (Berquin *et al.*, 1998, Bledsoe *et al.*, 2011, Castellanos *et al.*, 2002, Seidman *et al.*, 2005), to our knowledge this is the first study examining the neuroanatomical

correlates of time reproduction performances specifically in adults with ADHD. The relationship of the cerebellum and prefrontal cortex on timing tasks has been explored in recent studies that directly compared the performance of patients with lesions of either of these structures. The results suggest that, whereas lesions of the cerebellum directly affect the ability to encode temporal information, prefrontal lesions interfere with maintaining and monitoring these representations in working memory (Handy *et al.*, 2003). The basal ganglia have also been tied to the operation of an internal clock which contributes to the representations of the subjective passage of time (Ivry, 1996). Our results highlighting the involvement of the cerebellum, rather than prefrontal cortex or basal ganglia, might suggest that the deficit driving poor timing in adult with ADHD is linked to the encoding phase and not related to deficits in maintaining and monitoring temporal information in working memory. This is in line with the lack of a clear relationship between working memory and temporal reproduction (Mette *et al.*, 2015). Overall, grey matter abnormalities in the cerebellum might cause inefficiencies in frontocerebellar networks critical for time processing. For example, lobule V is part of the sensorimotor network receiving projections from primary motor and sensory cortices (M1, S1 and premotor cortex) dealing with sensorimotor integration and motor timing (Stoodley, 2012, Stoodley and Schmahmann, 2009). It is plausible that grey matter increase in lobule V causes difficulties in engaging this network optimally, therefore contributing to poor timing reproduction performance in adults with ADHD compared to typically developing controls.

A final aim of this study was to test temporal reproduction as a putative cognitive endophenotype for ADHD in adults. Interestingly, the performance of unaffected first degree relatives fell in between that of ADHD patients and of controls, though not statistically significantly different from either group. This is in line with the notion that as an endophenotype, a characteristic should present also in relatives of affected individuals but

milder (Almasy and Blangero, 2001, Gottesman and Gould, 2003). Therefore, our results suggest that time reproduction deficits might be a cognitive endophenotype for ADHD in adulthood. However, this significant result awaits further replication.

In conclusion, we have extended the literature from children to adults, to show that time reproduction performances were impaired in ADHD across different ages. Moreover, there was a statistical trend delineating a difference between relatives and controls, suggesting that time reproduction performances were in between ADHD and controls. This pattern of results is consistent with the idea that time reproduction might be a cognitive endophenotypes in adult ADHD. Finally, grey matter volume in the cerebellum, but not basal ganglia and prefrontal cortex, was associated with time reproduction performances (particularly in the ADHD group), such that the more grey matter volume in the cerebellar lobule V the poorer the timing performance. This is consistent with the hypothesis of ineffective pruning which might have an important etiological role in the symptomatology of adult ADHD; an hypothesis to be tested in future research.

**Declaration of interests**

ETB is employed half-time by GSK and half-time by the University of Cambridge; he holds stock in GSK. BJS consults for Cambridge Cognition, Peak, Servier and Lundbeck; she holds a grant from Janssen/J&J. UM has received honoraria for consultancy and speaking at conferences and travel expenses from Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pharmacia-Upjohn and UCB Pharma. The remaining authors reported no biomedical financial interests or potential conflicts of interest.



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**Table 1:** sample characteristics and clinical measures

	ADHD		Relatives		Controls		F (2,57)	<i>p</i> -value
	Mean	SD	Mean	SD	Mean	SD		
Age	32.2	10.31	38.85	15.31	32.55	5.8	2.245	<i>p</i> = 0.115
Gender % Female	15		50		35		5.550	<i>p</i> = 0.062 <sup>1</sup>
NART full IQ	115.26	6.15	116.59	5.28	119.49	3.27	3.679	<i>p</i> = 0.031 <sup>2</sup>
BAARS Current Total Symptoms	36.15	12.39	10.00	7.38	5.20	4.29	73.5	<i>p</i> < 0.001 <sup>23</sup>
BAARS Current Hyperactive/Impulsive	18.40	6.98	5.25	4.13	2.50	2.50	60.11	<i>p</i> < 0.001 <sup>234</sup>
BAARS Current Inattentive Symptoms	17.75	5.96	4.75	3.89	2.70	2.77	68.44	<i>p</i> < 0.001 <sup>23</sup>
BAARS Childhood Total Symptoms	41.35	11.93	14.20	10.28	4.85	6.65	73.78	<i>p</i> < 0.001 <sup>234</sup>
BAARS Childhood Hyperactive/Impulsive	20.65	6.23	6.60	4.45	2.15	3.44	79.45	<i>p</i> < 0.001 <sup>234</sup>
BAARS Childhood Inattentive Symptoms	20.70	6.04	7.60	6.23	2.70	4.07	56.57	<i>p</i> < 0.001 <sup>234</sup>

ADHD, attention-deficit/hyperactivity disorder; BAARS, Barkley Adult ADHD Rating Scale; NART, National Adult Reading Test.

<sup>1</sup>  $\chi^2$

<sup>2</sup> The ADHD group differs significantly from the controls.

<sup>3</sup> The ADHD group differs significantly from the relatives.

<sup>4</sup> Relatives differ significantly from controls.

**Table 2:** Mean and standard deviation of the absolute discrepancy score for the seven different target durations (averaged across trials) according to group.

Temporal reproduction task						
Durations	ADHD		Relatives		Controls	
	Mean	SD	Mean	SD	Mean	SD
500	208.13	126.99	157.61	100.00	146.24	68.62
1000	256.96	157.89	272.27	139.66	250.54	108.71
3000	650.27	371.89	627.46	303.12	494.09	223.70
6000	856.27	534.11	861.59	473.26	658.36	255.05
12000	1494.48	1082.65	1393.45	1139.36	804.14	485.11
18000	2546.90	1939.84	2302.58	1281.75	1570.66	784.43
24000	4031.72	3139.60	2924.64	1999.30	1608.75	726.06

*Note.* All values are in milliseconds.

### **Captions for figures**

**Figure 1:** Mean absolute magnitude of error in the time reproduction task according to target duration and group. Bars represent standard error of the mean (SEM).

**Figure 2:** Positive correlation between absolute discrepancy scores and grey matter volume estimates across groups, suggesting the more grey matter volume in the cerebellum (Right lobule V) the poorer is the performance in time reproduction abilities. No significant results were found in the prefrontal cortex and basal ganglia.



